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Health and Environmental Effects
Profile for Isophorone

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16. ABSTRACT The Health and Environmental Effects Profile for <u>Isophorone</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Isophorone</u> has been evaluated as a carcinogen. The human carcinogen potency factor (q₁*) for <u>Isophorone</u> is 4.1×10^{-2} (mg/kg/day)⁻¹ for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>Isophorone</u> is <u>1000</u>.			
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR ISOPHORONE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Isophorone is a clear, colorless liquid with a peppermint-like odor and a cooling taste (U.S. EPA, 1980a). It has a moderate vapor pressure of 0.38 mm Hg and a moderate solubility (12,000 mg/l) in water at 20°C (U.S. EPA, 1980a; Verschueren, 1983). As of January, 1985, only two companies manufactured isophorone in the United States, but the current production volume is not available. Isophorone is generally manufactured by the condensation of acetone in the presence of a base at high temperature and pressure. Commercial isophorone is ~96-98% pure and tends to discolor on prolonged storage (Papa and Sherman, 1981).

Isophorone is used primarily as a solvent for a large number of natural and synthetic polymers, resins, waxes, fats and oils. It is also used as a chemical intermediate for the synthesis of other chemicals (Papa and Sherman, 1981; U.S. EPA, 1980a).

The limited information available is not adequate to predict the fate and transport of isophorone in any environmental medium. Compared with information for air and soil, more information about the fate of isophorone in aquatic media are available. Based on its fate in aquatic media, it is anticipated that isophorone will not undergo significant photodegradation in the atmosphere. Significant amounts of isophorone may be removed from the atmosphere through photochemical smog formation (Levy, 1973; Suyama et al., 1983), but no kinetic data are available to predict the half-life for this reaction. Based on its physical properties, it has been speculated that significant amounts of isophorone will not be removed from the atmosphere through dry deposition or precipitation of atmospheric aerosols. Wet deposition, however, may be a significant physical removal mechanism for atmospheric isophorone.

Most studies conducted with mixed microorganisms indicate that isophorone is biodegradable in aquatic media (Tabak et al., 1981; U.S. EPA, 1983). From the estimated biotransformation rate constant (Mabey et al., 1981), the freshwater half-life for isophorone that is attributed to biodegradation is estimated to be ~10 days. Oxidation and hydrolysis are probably not important aquatic fate processes for isophorone (Callahan et al., 1979; Mabey et al., 1981). The role of photolysis in the degradation of isophorone in aquatic media is unclear, but is probably insignificant. From its estimated Henry's law constant, it has been speculated that the loss of isophorone through volatilization from aquatic media will be insignificant. Similarly, sorption of isophorone onto sediments and particulate matter will probably not be an important process. Isophorone is not expected to bioconcentrate significantly in aquatic organisms (Barrows et al., 1980).

In the absence of pertinent experimental data, it has been speculated from its fate in aquatic media that significant biodegradation of isophorone will occur in soil. Leaching of isophorone from soil to groundwater may occur if the biodegradation process in soil is not fast enough to compete with its leaching process. Isophorone is unlikely to volatilize significantly from soil.

No data regarding the monitoring of isophorone levels in the ambient air were located in the available literature; however, isophorone has been detected in many occupational atmospheres, although the levels in most cases were below the OSHA standard of 25 ppm (Code of Federal Regulations, 1981). The maximum concentration of isophorone reported in any occupational atmosphere was 25.7 ppm, which was reported from a silk screen printing operation at a company in Pittsburgh, PA (Kominsky, 1981). In a recent National Occupational Hazard Survey, 1,004,686 people were reported to be occupationally exposed to isophorone (NIOSH, 1985).

Isophorone has been detected in a few drinking water supplies in the United States with a reported maximum concentration of 9.5 $\mu\text{g}/\text{l}$ (U.S. EPA, 1980a). It has also been detected in drinking water from the New Orleans area (1.6-2.9 $\mu\text{g}/\text{l}$), Cincinnati, OH (0.02 $\mu\text{g}/\text{l}$) and Philadelphia, PA (trace) (U.S. EPA, 1980a; Suffet et al., 1980; Sheldon and Hites, 1979; Keith et al., 1976). Isophorone has also been detected in a few surface waters in the United States and Europe; the maximum reported isophorone concentration in any U.S. surface water was 3 $\mu\text{g}/\text{l}$ (Sheldon and Hites, 1979). Isophorone has also been detected in wastewater from a variety of industries (U.S. EPA, 1981), clogged water in a chemical dump site (Stonebraker and Smith, 1980) and in storm water runoff (Cole et al., 1984). The level of isophorone in the wastewater from a paint and ink formulation plant was reported to be as high as 44,000 $\mu\text{g}/\text{l}$ (U.S. EPA, 1981).

Pertinent data regarding the monitoring of isophorone levels in food were not located in the available literature; consequently, human exposure to isophorone from inhalation, ingestion or dermal contact cannot be estimated.

Acute LC_{50} or EC_{50} values for freshwater and marine species were generally 100-400 mg/l , with the exception of mysid shrimp, Mysidopsis bahia, which were unusually sensitive (96-hour LC_{50} = 12.9 mg/l) (U.S. EPA, 1980a). NOECs for growth reduction in chronic embryo larval tests were 14 mg/l in fathead minnows (Cairns and Nebeker, 1982) and 80-156 mg/l for sheepshead minnows (Ward et al., 1981). The NOEC for unspecified effects in Daphnia magna was 15 mg/l (Leblanc, 1980). Based on the limited information available, 15 mg/l isophorone appears to be a NOEC for freshwater fish and invertebrates.

Isophorone can be absorbed by the gastrointestinal tract, as indicated by the detection of parent compound and its metabolites in the urine of rats and rabbits after oral dosing (Dutertre-Catella et al., 1978). Absorption by the lungs and skin can be inferred from the systemic toxicity observed in animals after inhalation (Sections 5.5 and 5.6) and dermal exposure (Hazelton Labs, Inc. 1964a,b). Information regarding the distribution of isophorone was not located. Isophorone was metabolized by rats and rabbits to 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one by methyloxydation, to isophorol by reduction of the ketone group, to dihydroisophorone by dehydrogenation of the ring double bond and to cis- and trans-3,5,5-trimethylcyclohexanols by dismutation of dihydroisophorone (Dutertre-Catella et al., 1978; Truhaut et al., 1970). Unchanged isophorone and its metabolites were excreted in the urine of rats and rabbits, with isophorol, dihydroisophorone and the cis- and trans-trimethylcyclohexanols excreted as glucuronides. Unchanged isophorone was also eliminated in the expired air.

In a peer-reviewed draft of an NTP (1985) 103-week gavage study, it was concluded that there was some evidence that isophorone was carcinogenic to rats. The conclusion was based on findings of increased incidences of the relatively rare renal tubule cell adenomas and adenocarcinomas in male rats treated with 250 and 500 mg/kg/day, 5 days/week and the rare preputial gland carcinomas in males treated with 500 mg/kg/day, 5 days/week. NTP (1985) concluded that there was equivocal evidence that isophorone was carcinogenic to mice because of marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system in male mice treated with 500 mg/kg/day, 5 days/week and malignant lymphomas in male mice treated with 250 mg/kg/day, 5 days/week.

Isophorone was negative for reverse mutation in four strains of Salmonella typhimurium and for chromosome aberrations in Chinese hamster ovary cells in the presence or absence of S9 (NTP, 1985). Negative results were also obtained for the micronucleus test in male and female mice and for UDS in primary rat hepatocytes (CMA, 1984). A positive response was obtained for SCE in Chinese hamster ovary cells in the absence, but not in the presence of S9 (NTP, 1985). Although CMA (1984) obtained negative results for forward mutation using mouse lymphoma cells in the presence and absence of S9, NTP (1985) found a slight positive response in the same assay in the absence of S9 at much higher concentrations of isophorone.

No fetotoxic or teratogenic effects were observed in the offspring of rats and mice exposed by inhalation to isophorone at 0, 25, 50 or 115 ppm (0, 141, 283 or 550 mg/m³), 6 hours/day on days 6-15 of gestation.

In addition to the carcinogenic effects observed in rats and mice, NTP (1985) also found nonneoplastic effects of chronic oral exposure to isophorone. Compound-related reduced survival was observed in high-dose male rats. Increased incidences of kidney lesions consisting of tubular cell and renal pelvis epithelial hyperplasia, tubule mineralization and nephropathy, were observed at both doses in male and female rats. Dose-related increased incidences of fatty metamorphosis of the adrenal cortex in male rats and focal hyperplasia of the anterior pituitary in female rats were also considered to be treatment-related. Treated mice (both doses) had increased incidences of coagulative necrosis and hepatocytomegaly in the liver, hyperkeratosis of the forestomach and focal hyperplasia of the pituitary. High-dose mice had increased incidences of chronic focal inflammation of the kidney.

In a 13-week preliminary gavage study, no treatment-related effects were observed in rats treated at ≤ 500 mg/kg/day, 5 days/week (NTP, 1985). Rats, but not mice, were lethargic immediately after dosing with 1000 mg/kg day; some female rats and mice died. In a 90-day study, male rats exposed to 3000 ppm isophorone in the diet (250.5 mg/kg/day) had a significant, treatment-related decrease in mean body weight gain after 6 weeks; there was no effect on food consumption (AME, Inc., 1972a). No effects were observed at ≤ 1500 ppm (≤ 170.4 mg/kg/day). In dogs treated with 0, 35, 75 or 150 mg/kg/day of isophorone in gelatin capsules for 90 days, the only effect was soft and loose stools of dogs treated at 75 or 150 mg/kg/day (AME, Inc., 1972b). Values for the acute oral LD_{50} of isophorone in rats range from 1000-3450 mg/kg (Union Carbide and Carbon Corp., n.d.; Dow Chemical Co., 1962; Hazelton Labs, Inc. 1964a,b; Smyth et al. 1969, 1970; Bukhalovskii and Shugaev, 1976).

Subchronic inhalation exposure of rats and guinea pigs to isophorone at concentrations ≥ 100 ppm (≥ 565 mg/m³), 8 hours/day, 5 days/week for 6 weeks was associated with death, severe kidney and lung lesions and poor growth (Smyth et al., 1942). Liver and kidney lesions were also observed at 50 ppm (283 mg/m³); no effects were observed at 25 ppm (141 mg/m³). As discussed by U.S. EPA (1980a), subsequent evaluation of this study revealed that the isophorone used by Smyth et al. (1942) was impure; therefore, the dose-response data are seriously compromised. Inhalation exposure of rats to 0.208 mg/l (208 mg/m³), 6 hours/day, 5 days/week for 4 weeks was associated with transient nasal bleeding, hematological changes, decreased body weight gain and decreased absolute and relative liver weights (Hazelton Labs, Inc., 1968). The inhalation LC_{50} in rats was reported to be 7000 mg/m³ for 4 hours (Hazelton Labs, Inc., 1965a).

Inhalation exposure to 25 ppm (141 mg/m³) for 15 minutes produced eye, nose and throat irritation in humans; 10 ppm (57 mg/m³) was tolerable for 8 hours (Silverman et al., 1946). Hazelton Labs, Inc. (1965b) found that the odor threshold was <100 mg/m³, the eye and nose irritation thresholds were <359 mg/m³ and the throat irritation threshold was <199 mg/m³ for six humans exposed for 7 minutes to isophorone in an aerosol chamber.

A q_1^* value of 4.1×10^{-3} (mg/kg/day)⁻¹ was derived from the dose-response data for increased incidences of hepatic or integumentary system tumors in male mice treated by gavage with isophorone at 250 and 500 mg/kg/day, 5 days/week for 2 years in the NTP (1985) study. The q_1^* was recommended for estimating the increased lifetime risk of cancer for human exposure to isophorone. An F factor of 2.22×10^{-2} (mg/kg/day)⁻¹ was derived from the same data, placing isophorone in Potency Group 4; isophorone was given an IARC classification of C. Therefore, isophorone has a LOW Hazard Ranking under CERCLA.

An RQ of 1000 for chronic toxicity was based on the subchronic inhalation study in rats by Hazelton Labs, Inc. (1968).

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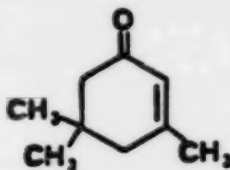
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstracts Service
EC ₅₀	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
i.p.	Intraperitoneal
K _{oc}	Soil sorption coefficient
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD ₅₀	Dose lethal to 50% of recipients
MATC	Maximum acceptable toxicant concentrations
MED	Minimum effective dose
NOEC	No-observed-effect concentration
POTW	Publicly owned treatment works
ppb	Parts per billion
PVC	Polyvinyl chloride
RQ	Reportable quantity
SCE	Sister chromatid exchange
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as isophorone is also called 3,5,5-trimethyl-2-cyclohexene-1-one; isooctaphenone; and isoacetophorone. The structure, empirical formula, molecular weight and the CAS Registry number for isophorone are as follows:



Empirical formula: $C_9H_{14}O$

Molecular weight: 138.2

CAS Registry number: 78-59-1

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Isophorone is a clear colorless liquid with a peppermint-like odor and a cooling taste (U.S. EPA, 1979, 1980a). Selected physical properties of isophorone are listed below:

Melting point:	-8.1°C	Papa and Sherman, 1981
Boiling point at 1 atm:	215.3°C	Papa and Sherman, 1981
Specific gravity, 20/20°C:	0.9229	Papa and Sherman, 1981
Flash point:	96.1°C	OHMTADS, 1985
Vapor pressure:		
20°C	0.38 mm Hg	Verschueren, 1983
25°C	0.44 mm Hg	U.S. EPA, 1980a
Vapor density:	4.77	Verschueren, 1983
Water solubility: at 20°C	12,000 mg/l	U.S. EPA, 1980a

Henry's Law Constant:	$5.76 \times 10^{-6} \text{ atm} \cdot \text{m}^3 \text{mol}^{-1}$	Papa and Sherman, 1981 (estimated)
Log K_{ow} :	1.7	Callahan et al., 1979 (estimated)

Isophorone is a cyclic α, β -unsaturated ketone. It reacts readily with hydrogen peroxide to form the 2,3-epoxy compound, which has the potential of forming hazardous peroxides on prolonged contact with air. It also undergoes reduction, oxidation and cyclo-addition reactions in the presence of a catalyst at high temperatures with or without pressure (Papa and Sherman, 1981). Isophorone is stable under normal atmospheric conditions and the reactions mentioned above are not significant under environmental conditions.

1.3. PRODUCTION DATA

As of January, 1985, isophorone was manufactured in the U.S. by Exxon Corp., Bayway, NJ, and Union Carbide Corp., Institute, WV (SRI, 1985). USITC (1985) also lists these two companies as the two U.S. manufacturers of isophorone in 1984. Since only two United States companies manufacture this chemical, data on its recent production volume are not available. In 1973, 35 million pounds of isophorone were produced in the United States (Papa and Sherman, 1981). According to the TSCA Inventory (U.S. EPA, 1977), the companies that imported isophorone in the United States in 1977 were Uguine Kuhlmann of America, Inc., Paramus, NJ; EM Laboratories, Inc., Elmsford, NY; Thorson Chemical Corp., New York, NY; B.P. North America Inc., New York, NY; and Rohm and Haas Co., Philadelphia, PA.

Isophorone is generally manufactured by two processes. In the older vapor-phase process, acetone vapor is passed over a catalyst bed of magnesium aluminate, zinc oxide-bismuth oxide or calcium oxide at 300-400°C and under pressure. In the modern liquid-phase process, acetone, water and potassium hydroxide are allowed to react at ~200°C and ~35 atm pressure.

Both processes produce substantial amounts of by-products and require distillation and acidic discoloration treatment for the purification of isophorone (Papa and Sherman, 1981). Commercial isophorone is ~96-98% pure, but contains the following impurities (U.S. EPA, 1980a):

B-isophorone	2-4%
mesitylene (1,3,5-trimethylbenzene)	trace
mesityl oxide	trace
phorone (2,6-dimethyl-2,5-heptadiene-4-one)	trace
isoxylitones	trace
water	trace

Isophorone tends to discolor on prolonged storage. Color formation can be prevented by treatment with p-toluene sulfonic acid, acidified fuller's earth, diazines or diisopropylamine (Papa and Sherman, 1981).

1.4. USE DATA

Isophorone is a powerful solvent for a large number of natural and synthetic polymers, resins, waxes, fats and oil; it is also used as a solvent for pesticide and herbicide formulation. It is exceptionally effective in bonding articles of PVC and polystyrene, and is used as a chemical intermediate for the synthesis of 3,5-xyleneol, 3,3,5-trimethylcyclohexanol and plant growth retardants (U.S. EPA, 1980a; Papa and Sherman, 1981).

1.5. SUMMARY

Isophorone is a clear, colorless liquid with a peppermint-like odor and a cooling taste (U.S. EPA, 1979, 1980a). It has a moderate vapor pressure of 0.38 mm Hg and a moderate solubility (12,000 mg/l) in water at 20°C (U.S. EPA, 1980a; Verschueren, 1983). As of January, 1985, only two companies manufactured this chemical in the United States and the current U.S. production volume of isophorone is not available. Isophorone is

generally manufactured by the condensation of acetone in the presence of a base at high temperature and pressure. Commercial isophorone is -96-98% pure and tends to discolor on prolonged storage (Papa and Sherman, 1981).

Isophorone is used primarily as a solvent for a large number of natural and synthetic polymers, resins, waxes, fats and oils. It is also used as a chemical intermediate for the synthesis of other chemicals (Papa and Sherman, 1981; U.S. EPA, 1980a).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

The available data regarding the fate of isophorone in the atmosphere are limited. The Sadtler U.V. spectra for isophorone in methanol solution shows that this compound has an absorption maximum at a wavelength of 235 nm; it absorbs very little at wavelengths >270 nm. Although Jennings (1965) showed that irradiation of isophorone in water or aqueous methanol led to the formation of a dimer, the possibility of dimer formation in the atmosphere is extremely unlikely for several reasons. Jennings (1965) conducted the reaction with light of wavelength >200 nm (Callahan et al., 1979) and at high isophorone concentrations ($\sim$ g/l). The reaction was also found to be dependent on the dielectric constant of the medium, and no dimerization reaction was observed with media of low dielectric constants. Since the available wavelengths in the troposphere are >290 nm, the dielectric constant of air is low and the concentration of isophorone in the atmosphere is also expected to be low, making the dimerization reaction extremely unlikely to occur in the atmosphere.

Isophorone is more likely to react with nitrogen oxides in the atmosphere in the presence of sunlight. The photochemical smog reactivity of isophorone was studied by Levy (1973). Isophorone was found to be of intermediate reactivity (compared with other organic solvents) with respect to the time for maximum NO_2 formation; the average time for the maximum NO_2 formation was ~ 130 minutes. The compound was highly reactive towards ozone and other oxidant formation; however, it was classified to be of low reactivity in terms of its ability to form formaldehyde and peroxy-compounds.

The photochemical reactivity of isophorone under UV irradiation in a smog chamber at initial isophorone and NO concentrations of 2 and 1 ppm, respectively, was studied by Suyama et al. (1983). The reactivity of isophorone in terms of the rate of disappearance of NO was assessed to be very high. No data regarding the rates of disappearance of isophorone as a result of photochemical smog reaction were given in either of the studies. Therefore, the atmospheric half-life of isophorone that is attributed to photochemical smog reactions cannot be estimated.

Quantitative estimations for the removal rate of atmospheric isophorone that is due to physical removal mechanisms cannot be made because of the lack of available information. Based on the vapor pressure of isophorone at 20°C and the equation given by Cupitt (1980), it is unlikely that significant amounts of atmospheric isophorone will be removed by adsorption onto aerosol particles. Similarly, removal of atmospheric isophorone by dry deposition is probably not significant. From the relatively moderate aqueous solubility of isophorone, it is speculated that wet deposition will remove significant amounts of isophorone from the atmosphere.

2.2. WATER

There is more information available regarding the fate and transport of isophorone in aquatic media than there is for its fate and transport in other media; however, it is still not possible to ascertain the most probable fate and transport mechanisms of isophorone in aquatic media. Mikami et al. (1981) found that isophorone degraded in a pure culture of Aspergillus niger and isolated four metabolites from this degradation reaction. The biodegradability test by Tabak et al. (1981), with domestic wastewater as microbial inoculum, demonstrated that the compound is significantly degradable and the microorganisms are capable of rapid adaptation. The

activated sludge treatment of two industrial influents at concentrations of 10 $\mu\text{g/l}$ showed little biodegradation of the compound, whereas aerated lagoon treatment of one industrial effluent at a concentration of 3 $\mu\text{g/l}$ resulted in ~33% removal of the compound (Patterson and Kodukala, 1981). The study by Feller et al. (1979), on the other hand, showed a substantial removal of isophorone from a POTW operated with a conventional activated sludge treatment process. The treatment of industrial effluents from Union Carbide Corporation with unacclimated activated sludge produced 42% biodegradation of isophorone after 20 days (U.S. EPA, 1983). It is difficult to draw conclusions about the biodegradation potential of this compound in natural aquatic systems from the above studies. Mabey et al. (1981) estimated the biotransformation rate constant for isophorone in natural aquatic media to be $3 \times 10^{-9} \text{ ml cell}^{-1} \text{ hr}^{-1}$. Assuming that the concentration of microorganisms in freshwater is $\sim 10^6 \text{ cell ml}^{-1}$, the half-life for biodegradation in freshwater is estimated to be ~10 days.

Oxidation and hydrolysis are probably not important aquatic fate processes for isophorone (Callahan et al., 1979; Mabey et al., 1981), and the role of photolysis in the determination of the aquatic fate of isophorone remains uncertain. Although the irradiation of aqueous solutions of isophorone at high concentrations ($\sim \text{g/l}$) with light of wavelength $>200 \text{ nm}$ resulted in dimer formation (see Section 2.1.), it is not likely that such a reaction will take place in natural aquatic media where the available wavelengths are much longer ($\sim >290 \text{ nm}$) and the concentration of the substrate is much lower.

Pertinent data regarding the volatilization probability of isophorone from aquatic media could not be located in the available literature. Based on the Henry's law constant (see Section 1.2.) and volatility characteristics associated with various Henry's Law constant (Lyman et al., 1982),

volatilization of isophorone from aquatic media is not expected to be significant. The regression equation, $\log K_{oc} = -0.55 \log S + 3.64$ (Lyman et al., 1982), where S is the aqueous solubility in mg/l, can be used to estimate the K_{oc} of compounds; the K_{oc} for isophorone is estimated to be 25. Therefore, sorption of isophorone into sediments and particulate matter will probably not be an important process and the compound will remain in solution in aquatic media.

In a continuous flow system using an exposure period of 14 days, the bioaccumulation potential of isophorone at an initial concentration of ~ 92.4 $\mu\text{g/l}$ was experimentally measured in bluegill sunfish, Lepomis macrochirus (Barrows et al., 1980). The BCF was measured to be 7, but it can also be estimated from the K_{ow} value using the equation, $\log \text{BCF} = 0.76 \log K_{ow} - 0.23$ (Lyman et al., 1982). The estimated BCF by this method is 12. Therefore, isophorone is not expected to bioconcentrate significantly in aquatic organisms.

2.3. SOIL

Pertinent data regarding the fate and transport of isophorone in soil could not be located in the available literature. Based on its fate in aquatic media it is speculated that isophorone will biodegrade in soil. Volatilization of isophorone from soil is expected to be insignificant. Based on its moderate water solubility and low K_{oc} (see Section 2.2.), leaching of isophorone from soil to groundwater is expected to occur if the biodegradation process in soil is not fast enough to compete with leaching. Isophorone from soil is also expected to be transported to surface water from storm water runoff (Cole et al., 1984).

2.4. SUMMARY

The limited information available in the literature is not adequate to predict the fate and transport of isophorone in any environmental medium. Compared with information for air and soil, more information about the fate of isophorone in aquatic media are available. Based on its fate in aquatic media, it is anticipated that isophorone will not undergo significant photodegradation in the atmosphere. Significant amounts of isophorone may be removed from the atmosphere through photochemical smog formation (Levy, 1973; Suyama et al., 1983), but no kinetic data are available to predict the half-life for this reaction. Based on its physical properties, it has been speculated that significant amounts of isophorone will not be removed from the atmosphere through dry deposition or precipitation of atmospheric aerosols. Wet deposition, however, may be a significant physical removal mechanism for atmospheric isophorone.

Most studies conducted with mixed microorganisms indicate that isophorone is biodegradable in aquatic media (Tabak et al., 1981; U.S. EPA, 1983). From the estimated biotransformation ratio constant (Mabey et al., 1981), the freshwater half-life for isophorone that is attributed biodegradation is estimated to be ~10 days. Oxidation and hydrolysis are probably not important aquatic fate processes for isophorone (Callahan et al., 1979; Mabey et al., 1981). The role of photolysis in the degradation of isophorone in aquatic media is unclear, but is probably insignificant. From its estimated Henry's law constant, it has been speculated that the loss of isophorone through volatilization from aquatic media will be insignificant. Similarly, sorption of isophorone onto sediments and particulate matter will probably not be an important process. Isophorone is not expected to bioconcentrate significantly in aquatic organisms (Barrows et al., 1980).

In the absence of pertinent experimental data, it has been speculated from its fate in aquatic media that significant biodegradation of isophorone will occur in soil. Leaching of isophorone from soil to groundwater may occur if the biodegradation process in soil is not fast enough to compete with its leaching process. Isophorone is unlikely to volatilize significantly from soil.

3. EXPOSURE

3.1. AIR

Pertinent data regarding the monitoring of isophorone levels in the ambient air could not be located in the available literature. The production and user sites are expected to be the primary sources by which isophorone is emitted to the atmosphere. Harrison et al. (1985) detected 490 $\mu\text{g/g}$ isophorone in the fly ash collected from an electrostatic precipitator from a coal-fired power station in New Mexico. Therefore, coal-burning power plants may also be a source of atmospheric isophorone.

Isophorone has been detected in many occupational atmospheres. In a silk screen printing operation at a company in Pittsburgh, PA, concentrations of isophorone up to 25.7 ppm were detected (Kominsky, 1981). Lee and Frederick (1982) detected concentrations of isophorone ranging from 0.7-14 ppm in breathing zone samples from a decal manufacturing plant in Ridgefield, NJ. Bierbaum and Parnes (1982) reported that the personal and general area samples taken from an electrical division of a brass company in South Windsor, CN, showed levels of isophorone well below the OSHA standard of 25 ppm (Code of Federal Regulations, 1981). The levels of isophorone in the breathing zone and area samples of various job sites and general air of a screen printing plant are shown in Table 3-1.

Salisbury (1984) also detected isophorone concentrations at levels <25 ppm in personal and general area samples from a screen printing plant.

The levels of isophorone in the breathing zone air samples from a isophorone manufacturing plant (Exxon Chemical) were reported to range from 0.01-0.63 ppm with a mean value of 0.07 ppm (U.S. EPA, 1982). In a recent National Occupational Hazard Survey, NIOSH (1985) reported that 1,004,686 people are occupationally exposed to isophorone.

TABLE 3-1
Isophorone Levels in Breathing Zone, Area Samples
and General Air of a Screen Printing Plant*

Job Site	Mean TWA Concentration (ppm)		
	Breathing Zone	Area Sample	General Air
Printing press	23	16	NR
Automatic dryer	9.5	12.5	NR
Manual drying	15	14.5	3.5
Paint mixing	17.8	7.5	NR
Screen wash	8.3	7.1	NR

*Source: Samimi, 1982

NR = Not reported

3.2. WATER

Isophorone has been detected in several samples of drinking water in the United States. The U.S. EPA measured isophorone levels in finished drinking water in the New Orleans area (Keith et al., 1976). The levels of isophorone at the Carrollton Water Treatment Plant and two other treatment sites in Jefferson Parish, were reported to be 1.6, 2.8 and 2.9 $\mu\text{g}/\text{l}$, respectively. In a 1974 survey of finished water from 10 cities, isophorone was detected at a concentration of 0.02 $\mu\text{g}/\text{l}$ in Cincinnati, OH, while none was detected in water from Miami, FL; Seattle, WA; Ottumwa, IA; Philadelphia, PA; Tucson, AZ; New York, NY; Lawrence, MA; Grand Forks, ND; and Terrebonne Parish, LA (U.S. EPA, 1980a). A survey of drinking water conducted in 1976 and 1977 from the Torresdale Water Treatment Plant in Philadelphia, PA, however, showed that isophorone was present (Suffet et al., 1980; Hites, 1979; Sheldon and Hites, 1979). The maximum concentration of isophorone in U.S. drinking water has been reported to be as high as 9.5 $\mu\text{g}/\text{l}$ (U.S. EPA, 1980a).

Isophorone has been detected in surface water in the United States and in Europe. In a survey test of Delaware River water conducted during August, 1976-March, 1977, trace amounts of isophorone were detected during the winter months at river mile 78 (Hites et al., 1979; Sheldon and Hites, 1978). A subsequent (August, 1977-March, 1978) survey test of the same river detected isophorone at a concentration of 3 $\mu\text{g}/\text{l}$ at river mile 106. The source of the isophorone was thought to be a wastewater treatment plant receiving industrial wastes. The level of isophorone downstream from this point decreased to 0.6 $\mu\text{g}/\text{l}$ at river mile 108 and finally none was detected at river mile 118 (Sheldon and Hites, 1979). Isophorone was

detected in 1 surface water of 14 surface and groundwater samples monitored in England (Fielding et al., 1981). Meijers and Van der Leer (1976) reported the presence of isophorone in the River Maas at Brakel, the Netherlands.

The primary source of isophorone in surface waters and finished drinking waters is probably industrial wastewaters, since isophorone has been detected in industrial wastewaters. Jungclaus et al. (1976) detected isophorone at a concentration of 40 $\mu\text{g/l}$ (40 ppb) in wastewater from an automobile tire plant. Isophorone in the concentration range of 19-49 $\mu\text{g/l}$ has been detected in standing water samples inside a waste disposal site in Bullitt County, KY (Stonebraker and Smith, 1980). In shale oil wastewater, the concentration of isophorone has been reported to range between 340 and 5800 $\mu\text{g/l}$ (Hawthorne and Sievers, 1984). The influent and effluent isophorone concentrations in Philadelphia's Northeast Sewage Treatment plant have been reported to be 100 and 10 $\mu\text{g/l}$, respectively (Sheldon and Hites, 1979). The concentration of isophorone in the influent water of an unnamed sewage treatment plant was reported to be <10 $\mu\text{g/l}$; however, the frequency of occurrence of isophorone in influent water was reported to be 17% (Feiler et al., 1979). The concentrations of isophorone in raw industrial wastewater have been reported to range between none detected and 44,000 $\mu\text{g/l}$ (U.S. EPA, 1981), while in treated wastewater, the concentrations of isophorone have been reported to range between none detected and 560 $\mu\text{g/l}$ (U.S. EPA, 1981). In one storm water runoff sample from the Washington, DC area, isophorone was detected at a concentration of 10 $\mu\text{g/l}$ (Cole et al., 1984).

3.3. FOOD

Pertinent data regarding the levels of isophorone in food could not be located in the available literature.

3.4. SUMMARY

Pertinent data regarding the monitoring of isophorone levels in the ambient air could not be located in the available literature; however, isophorone has been detected in many occupational atmospheres, although the levels in most cases were below its OSHA standard of 25 ppm (Code of Federal Regulations, 1981). The maximum reported concentration of isophorone in any occupational atmosphere was 25.7 ppm, which was reported from a silk screen printing operation at a company in Pittsburgh, PA (Kominsky, 1981). In a recent National Occupational Hazard Survey, ~1,004,686 people were reported to be occupationally exposed to isophorone (NIOSH, 1985).

Isophorone has been detected in a few U.S. drinking water supplies, with a reported maximum concentration of 9.5 $\mu\text{g}/\text{l}$ (U.S. EPA, 1980a). It has also been detected in drinking water from the New Orleans area (1.6-2.9 $\mu\text{g}/\text{l}$), Cincinnati, OH (0.02 $\mu\text{g}/\text{l}$) and Philadelphia, PA (trace) (U.S. EPA, 1980a; Suffet et al., 1980; Sheldon and Hites, 1979; Keith et al., 1976). Isophorone has also been detected in a few surface waters in the United States and Europe; the maximum reported isophorone concentration in any U.S. surface water was 3 $\mu\text{g}/\text{l}$ (Sheldon and Hites, 1979), although higher levels probably exist. Isophorone has been detected in wastewaters from a variety of industries (U.S. EPA, 1981), clogged water in a chemical dump site (Stonebraker and Smith, 1980) and in storm water runoff (Cole et al., 1984). The level of isophorone in the wastewater from a paint and ink formulation plant was reported to be as high as 44,000 $\mu\text{g}/\text{l}$ (U.S. EPA, 1981).

Pertinent data regarding the monitoring of isophorone levels in food could not be located in the available literature. Human exposure of isophorone from inhalation, ingestion or dermal contact cannot be estimated from the limited data available.

4. PHARMACOKINETICS

4.1. ABSORPTION

Quantitative data regarding the absorption of isophorone were not located; however, Dutertre-Catella et al. (1978) detected unchanged isophorone and its metabolites in the urine of rats and rabbits 24 hours following oral dosing with isophorone (Section 4.3!). These results indicate that isophorone was absorbed by the gastrointestinal tract. Absorption of isophorone by the gastrointestinal tract and the lungs can also be inferred from the systemic toxicity observed in animals following oral and inhalation exposure (Sections 5.5. and 5.6.).

Dow Chemical Co. (1962) found no indication that toxic amounts of isophorone were absorbed by the skin of rabbits. Hazelton Labs, Inc. (1964a,b), however, reported that 1/4 rabbits treated dermally with 3160 mg/kg had depression, labored breathing, sprawling and depressed reflexes; these are typical signs of toxicity following oral or inhalation exposure to isophorone.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of isophorone could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

The in vivo metabolism of isophorone has been studied in rabbits and rats (Truhaut et al., 1970; Dutertre-Catella et al., 1978). Rabbits were administered isophorone by gavage at a dose of 1 g/kg, followed by administration of 20 ml of water. Rats were treated by gavage with isophorone in olive oil at a dose of 1 g/kg. For rabbits, the urine collected 24 hours after treatment was found to contain unchanged isophorone, 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one and glucuronic acid conjugates of 3,5,5-trimethyl-2-cyclohexene-1-ol (isophorol), 3,5,5-trimethylcyclohexanone

(dihydroisophorone) and cis- and trans-3,5,5-trimethyl cyclohexanols. The rat urine contained the same glucuronide conjugates as the rabbit urine, but in different proportions: much more dihydroisophorone and less isophorol were found in the rat urine than in the rabbit urine. The expired air collected 6 hours after treatment contained unchanged isophorone.

Therefore, metabolism of isophorone by rats and rabbits involved methyl-oxidation to 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one, reduction of the ketone groups to a isophorol, which was excreted as a glucuronide, and hydrogenation of the double bond in the ring to form dihydroisophorone, also excreted as a glucuronide. Dutertre-Catella et al. (1978) suggested that the cis- and trans-3,5,5-trimethylcyclohexanols arose from dismutation of dihydroisophorone.

4.4. EXCRETION

Quantitative data regarding the excretion of isophorone could not be located in the available literature. In the Dutertre-Catella et al. (1978) study (see Section 4.3.), unchanged isophorone, isophorol, dihydroisophorol, 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one and cis- and trans-3,5,5-dimethylcyclohexanols were detected in the urine of rats and rabbits 24 hours after an oral dose of isophorone. The expired air contained unchanged isophorone 6 hours after dosing.

4.5. SUMMARY

Isophorone can be absorbed by the gastrointestinal tract, as indicated by the detection of parent compound and its metabolites in the urine of rats and rabbits after oral dosing (Dutertre-Catella et al., 1978). Absorption by the lungs and skin can be inferred from the systemic toxicity observed in animals after inhalation (Sections 5.5. and 5.6.) and dermal exposure (Hazelton Labs, Inc., 1964a,b). Information regarding the distribution of

isophorone was not located. Isophorone was metabolized by rats and rabbits to 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one by methyloxylation, to isophorol by reduction of the ketone group, to dihydroisophorone by dehydrogenation of the ring double bond and to cis- and trans-3,5,5-trimethylcyclohexanols by dismutation of dihydroisophorone (Dutertre-Catella et al., 1978; Truhaut et al., 1970). Unchanged isophorone and its metabolites were excreted in the urine of rats and rabbits with isophorol, dihydroisophorone and the cis- and trans-trimethylcyclohexanols excreted as glucuronides. Unchanged isophorone was also eliminated in the expired air.

5. EFFECTS

5.1. CARCINOGENICITY

An NTP (1985) carcinogenesis study of isophorone in rats and mice was available as a peer-reviewed draft. In this study, groups of 50 male and 50 female Fischer 344/N rats and 50 male and 50 female B6C3F1 mice were treated by gavage with isophorone (94-97% pure) in corn oil at doses of 250 or 500 mg/kg/day, 5 days/week for 103 weeks. Similar groups of rats and mice were treated with corn oil alone. Surviving animals were killed at 105 weeks. Complete necropsies and comprehensive histological examinations were performed on all rats that died during the study (unless precluded by advanced autolysis or cannibalism), that were killed in extremis during the study or that were killed at the end of the study.

For rats, survival of high-dose males was significantly ($p < 0.001$) reduced compared with controls after 96 weeks. Although the reduced survival was considered to be compound-related, the decline occurred sufficiently late in the study for the detection of late developing tumors. There was an overall decrease in survival of female rats that was due to several accidental death by gavage error. Increases in the incidences of tumors that were considered significant or noteworthy are presented in Table 5-1. Tumor incidences were analyzed statistically by three methods, which are described in the footnotes to Table 5-1. Male rats had an increased incidence (adjusted for intercurrent mortality) of tubular cell adenoma or adenocarcinoma (combined) of the kidney that was significant for the high-dose group by the life table test and significant for dose-related trend by the life table and incidental tumor tests; however, the overall incidence was not significant by the Cochran-Armitage or Fisher Exact tests. Although the incidence of kidney tumors was low, the occurrence was noteworthy because kidney tumors were rarely observed in this strain of rats; direct

TABLE 5-1

Incidence of Treatment-Related Tumors in Male Fischer 344/N Rats and Male B6C3F₁ Mice Treated by Gavage with Isophorone (94-97% pure) in Corn Oil for 103 Weeks and Observed for an Additional 2 Weeks^a

Species	Dose ^b (mg/kg/day)	Target Organ	Tumor Type	Tumor Incidence		p Values ^c		Cochran-Armitage and Fisher Exact
				Overall Rate ^c	Adjusted Rate (%) ^d	Life Table Tests	Incidental Tumor Tests	
Rat	0			0/50	0.0	0.014	0.034	0.101
	250	kidney	tubular cell adenoma or adeno- carcinoma	3/50	9.1	0.120	0.120	0.121
	500			3/50	12.0	0.025	0.073	0.121
Rat	0			0/50	0.0	0.002	0.019	0.006
	250	preputial gland	carcinoma	0/50	0.0	f/ f/	f/ f/	f/ f/
	500			5/50	17.9	0.012	0.068	0.028
Rat	0			4/50	12.1	0.027	0.059	0.326
	250	pancreas	acinar cell adenoma	9/50	26.3	0.114	0.102	0.117
	500			6/50	34.6	0.045	0.086	0.370
Mouse	0			18/48	58.5	0.100	0.027	0.025
	250	liver	hepatocellular adenoma or carcinoma	18/50	76.0	0.358N	0.420N	0.522N
	500			29/50	90.3	0.150	0.036	0.033
Mouse	0			6/48	24.6	0.073	0.034	0.033
	250	Integumentary system	Fibroma, sarcoma, fibrosarcoma or neurofibrosarcoma	8/50	31.3	0.548	0.452	0.419
	500			14/50	45.2	0.108	0.058	0.048
Mouse	0			7/48	35.4	0.204N	0.253N	0.316N
	250	hematopoietic system	malignant lymphoma	10/50	62.5	0.046	0.067	0.013
	500			5/50	10.2	0.272N	0.320	0.351N

TABLE 5-1 (cont.)

	Quality of Evidence
Strengths of Study:	The compound was administered by a relevant route to both sexes (female animals did not have increased incidences of treatment-related tumors) of two species (rats, mice) at two dose levels for the lifespan. Comprehensive histological examination and appropriate statistical analyses were performed.
Weakness of Study:	The survival of high-dose male rats was low, partially because of gavage accidents; however, the decline in survival occurred late in the study. The overall survival of control and treated male mice (partially because of fighting) and treated female rats (partially because of gavage accidents) was low.
Overall Adequacy:	Adequate.

^aSource: MTP, 1985

^bDosing was 5 days/week

^cNumber of animals with tumors/number of animals examined at this site

^dKaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality

^eNext to the control incidence are the p values associated with the trend test. Next to the dosed group incidence are the p values corresponding to pairwise comparisons between that dosed group and the controls. The life table test regards tumors in animals dying before terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage test for dose-related trend (p value next to control incidence) and Fisher Exact test (p values next to dosed group incidence) compare directly with the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by N.

^fNo p value is reported because no tumors were observed in the 250 mg/kg/day and vehicle control groups.

comparison of the incidence in the low- and high-dose groups with historical controls (0.4%) indicated a significant increase ($p=0.002$) by the Fisher Exact test. The increased incidence of carcinoma of the preputial gland showed a significant dose-related trend by all statistical methods, and was significantly increased in the high-dose group above the control incidence by the life table and Fisher Exact tests. Tumors of the preputial gland have been observed at a very low incidence (12/1094) in historical corn oil vehicle control rats in NTP studies; therefore, NTP (1985) stated that the effect may be compound-related. The adjusted incidence of acinar cell carcinoma of the pancreas was significantly increased in the high dose males compared with controls and followed a significantly positive dose-related trend by the life table tests alone. Although the higher incidence of these tumors in dosed rats suggests a compound-related effect, the incidences of acinar cell tumors in concurrent vehicle controls (4/50) and in historical, corn oil vehicle controls (3.3%) were relatively high. NTP (1985) suggested the possibility that isophorone was acting as a cocarcinogen or promotor of the effect of corn oil. No significantly increased incidences of tumors were observed in female rats. NTP (1985) concluded that there was some evidence of carcinogenicity in rats because of the increased incidences of the relatively rare renal tubular cell adenomas and adenocarcinomas in males treated with 250 or 500 mg/kg/day and of the rare preputial gland carcinomas in males treated with 500 mg/kg/day.

For mice, overall survival of vehicle control and dosed males was reduced, primarily because of fighting; however, sufficient numbers from all male groups were considered to be at risk for late-developing tumors. For dosed females, there was a significant ($p<0.05$) trend for improved

survival relative to controls. Increases in the incidence of tumors that were considered significant or noteworthy and the statistical methods of analysis are presented in Table 5-1. The incidences of hepatocellular adenoma or carcinoma (combined) and the incidences of fibromas, sarcomas, fibrosarcomas or neurofibrosarcomas (combined) of the integumentary system in male mice showed significant positive dose-related trends and were significantly greater than controls in the high-dose groups, when analyzed by the incidental tumor, the Cochran-Armitage and the Fisher Exact tests. The incidence of lymphoma was increased significantly in low-dose male mice compared with the control by the life table test and the Fisher Exact test; however, the Cochran-Armitage, incidental tumor and life table tests indicated a negative dose-related trend since the incidence of lymphoma in high-dose males was lower than the control incidence. No significant increased incidences of tumors were observed in female mice. NTP (1985) concluded that there was equivocal evidence of carcinogenicity in mice because of the marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system in high-dose males and of malignant lymphomas in low-dose males.

5.2. MUTAGENICITY

Isophorone has been tested for mutagenicity and genotoxicity by NTP (1985) and CMA (1984) (Table 5-2). Negative results were obtained in the reverse mutation assay using four strains of Salmonella typhimurium in the presence and absence of S-9 (NTP, 1985). CMA (1984) reported that isophorone was negative in a forward mutation assay using mouse lymphoma cells in the presence and absence of S-9, while NTP (1985) found a slightly positive response in the absence of S-9 in the same assay using much higher concentrations of isophorone. Negative results were obtained for the micronucleus

TABLE 5-2
Mutagenicity Testing of Isophorone

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<i>Salmonella</i> <i>typhimurium</i> TA100, TA1535, TA1537, TA98	94-97%	plate incorporation	33-3300 µg/plate	±S-9 from rats or hamsters	-	Negative with or without activation in all strains regardless of source of S-9	NTP, 1985
Forward mutation	L5178Y/TK ⁺ / mouse lymphoma cells	94-97%	cell culture	400-1200 µg/ml	none	+	The response was weakly positive at ≥600 µg/ml	NTP, 1985
Forward mutation	L5178Y/TK ⁺ / mouse lymphoma cells	NR	cell culture	0.067-10 µg/ml (-0.06-9 µg/ml)	±S-9	-	NC	CMA, 1984
UDS	rat primary hepatocytes	NR	cell culture	0.005-0.40 µg/ml	NA	-	NC	CMA, 1984
SCE	Chinese hamster ovary cells	94-97%	cell culture	160-1000 µg/ml	±S-9	±	The response was positive without S-9 at ≥500 µg/ml	NTP, 1985
Chromosome aberrations	Chinese hamster ovary cells	94-97%	cell culture	250-1600 µg/ml	±S-9	-	NC	NTP, 1985
Micronucleus test	Male and female CD-1 mouse erythrocytes	NR	i.p. injection	0.54 mg/kg	NA	-	NC	CMA, 1984

NC = No comment; NA = not applicable

test in male and female mice, for UDS in rat primary hepatocytes (CMA, 1984) and for chromosome aberrations in Chinese hamster ovary cells with and without S-9 (NTP, 1985). A positive response for SCE was obtained in Chinese hamster ovary cells in the absence, but not in the presence of S-9 (NTP, 1985).

5.3. TERATOGENICITY

CMA (1984) reported that Exxon Biomedical Sciences was preparing a report of a teratology study of isophorone; the results were summarized briefly by U.S. EPA (1985). Groups of 22 pregnant Fischer 344 rats and 22 pregnant CD-1 mice were exposed by inhalation to isophorone at concentrations of 0, 25, 50 or 115 ppm (0, 141, 283 or 650 mg/m³), 6 hours/day on days 6-15 of gestation. The rats and mice were sacrificed on days 20 and 18 of gestation, respectively. There were no differences in implantation sites and no fetal abnormalities in either species at any exposure level. Rat dams had dose-related increases in alopecia at unspecified doses, reduced body weights on days 12 and 15 of gestation at 115 ppm and reduced food consumption at 115 ppm. Mouse dams had decreased body weights at 115 ppm. Under the conditions of this study, therefore, isophorone was not teratogenic or fetotoxic even at exposure levels that were toxic to dams.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of isophorone could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The NTP (1985) carcinogenicity study of isophorone (see Section 5.1.) also provided information regarding nonneoplastic effects of chronic oral exposure to isophorone. For rats, there were no clinical signs of toxicity throughout the 103-week study. Body weight gains of high dose (500 mg/kg/day) males and females were reduced slightly (5-8%) compared with controls.

As discussed in Section 5.1., high-dose male rats had a compound-related reduced survival rate, while female rats had an overall reduced survival, which was due to several deaths by gavage error. In addition to the carcinogenic effects, several compound-related nonneoplastic histopathological lesions were observed. In the kidney, tubular cell hyperplasia, possibly a preneoplastic lesion, and epithelial hyperplasia of the renal pelvis were observed in low- and high-dose males and high-dose females, but not in controls. Relative to controls, increased incidences of tubule mineralization in dosed males and of nephropathy in dosed females were observed. Male rats had a dose-related increased incidence of fatty metamorphosis of the adrenal cortex, while female rats had a dose-related increased incidence of focal hyperplasia of the anterior pituitary. Statistical analyses of the incidences of nonneoplastic lesions were not performed.

For mice, no clinical signs of toxicity were observed (NTP, 1985). High-dose (500 mg/kg/day) female mice had a slightly reduced (5%) body weight gain compared with controls, but body weights were comparable among control and dosed males. Survival of all groups of male mice was reduced, which was partly due to fighting, but survival of dosed females was higher than controls. Several nonneoplastic lesions occurred with increased incidences and were considered to be compound-related. In the liver, there were increased incidences of coagulative necrosis and hepatocytomegaly in male mice at both 250 and 500 mg/kg/day. Low- and high-dose males and high-dose females had increased incidences of hyperkeratosis of the forestomach. High dose male mice had an increased incidence of chronic focal inflammation of the kidney, while low- and high-dose females had increased incidences of focal hyperplasia of the pituitary. Statistical analyses of the incidences of these lesions were not performed.

NTP (1985) also conducted preliminary 13-week studies, in which groups of 10 male and 10 female Fischer 344/N rats and B6C3F1 mice were treated by gavage with isophorone in corn oil. Doses were 0, 62.5, 125, 500 or 1000 mg/kg/day, 5 days/week. Animals were observed daily and weighed weekly. Complete gross necropsies were performed on all animals that died during the study or were killed at the end of the study, while comprehensive histological examinations were performed only in high-dose and control animals. No dose-related effects on body weight gain were observed in rats or mice. The deaths of one female rat and three female mice at 1000 mg/kg/day, were considered to be compound-related. Deaths occurred in other groups of mice but were attributed to gavage errors. Rats, but not mice, treated with 1000 mg/kg/day were lethargic after dosing. No other effects were observed.

NTP (1985) conducted 16-day gavage studies of isophorone in rats and mice. Groups of five male and five female Fischer 344/N rats and B6C3F1 mice were treated by gavage with isophorone in corn oil at 0, 125, 250, 500, 1000 or 2000 mg/kg/day, 5 days/week for ~2 weeks (12 doses in 16 days). No treatment-related effect on body weight was observed for mice, but rats treated with 1000 or 2000 mg/kg/day had reduced body weights (6.7-25.2% lower than controls). One male rat, four female rats and all mice treated with 2000 mg/kg/day died. Rats in all dosed groups were lethargic after dosing. Mice treated with 1000 mg/kg/day staggered after dosing. Gross necropsy of all animals and comprehensive histological examination of selected animals at 1000 and 2000 mg/kg/day revealed no compound-related lesions in rats or mice.

AME, Inc. (1972a) conducted a subchronic feeding study of isophorone in rats for the Rohm and Haas Company. Groups of 20 male and 20 female CFE weanling rats were maintained on diets containing 0, 750, 1500 or 3000 ppm

isophorone for 90 days. Based on weekly determinations of body weight gain, food consumption and compound consumption, the dietary levels were equivalent to TWA dosages of 0, 61.1, 123.1 or 250.5 mg/kg/day, respectively, for males, and 0, 82.7, 170.4 or 323.8 mg/kg/day, respectively, for females. Males treated at 3000 ppm (250.5 mg/kg/day) had a significant ($p < 0.01$), treatment-related decrease in mean body weight gain after 6 weeks; no effect on food consumption was observed. No effects on appearance or behavior, hematological, clinical chemistry or urinalysis parameters, gross pathology or organ weights were found. Histological examination of major organs of the high dose and control groups and of the liver and kidneys of the low and intermediate dose groups revealed no treatment-related lesions.

AME, Inc. (1972b) conducted a subchronic oral study of isophorone in dogs for the Rohm and Haas Company. Groups of four male and four female beagle dogs were treated with isophorone in gelatin capsules, once daily, 7 days/week for 90 days at dosages of 0, 35, 75 or 150 mg/kg/day. Dogs treated with 75 or 150 mg/kg/day had soft and loose stools; no other effects on general appearance or behavior were observed. No effects on food consumption and body weight gain, hematological, clinical chemistry and urinalysis parameters, gross pathology and organ weights were observed. Comprehensive histological examinations of controls and high dose dogs and microscopic examinations of the livers and kidneys of the low and intermediate dose groups revealed no treatment-related lesions.

No chronic inhalation studies of isophorone were located; however, two subchronic inhalation studies were available. Smyth et al. (1942) exposed groups of 10 male Wistar rats and 10 guinea pigs (males and females) by inhalation to commercial samples of isophorone at concentrations of 0, 25, 50, 100, 200 or 500 ppm (0, 141, 283, 565, 1130 or 2826 mg/m³), 8 hours/day, 5 days/week for 6 weeks. No distinction between rats and guinea pigs

was made in reporting the results. At 100, 200 and 500 ppm, 2/16, 3/18 and 9/20 animals died. Animals that died had severe kidney lesions (congestion, granular secretion, cloudy swelling, degeneration and necrosis) and lung lesions (congestion, red blood cells in alveoli, desquamation of the bronchiol epithelium and pneumonia). Animals exposed to 500 ppm had nose and eye irritation, poor growth, an increased percentage of neutrophils and a decreased percentage of lymphocytes, albuminuria and pathological changes in the liver (1/8 animals examined had congestion and cloudy swelling) and kidney (dilation of Bowman's capsule and cloudy swelling of the convoluted tubular epithelium in 6/9 animals examined). At 100 and 200 ppm, animals that survived had poor growth and kidney pathology, but no liver lesions. At 50 ppm, 1/6 animals had liver pathology and 4/6 had kidney lesions. No effects were observed at 25 ppm.

As discussed in U.S. EPA (1980a), the concentrations of isophorone in air reported by Smyth et al. (1942) could not possibly be attained under the conditions employed. The material used by Smyth et al. (1942) was impure, containing compounds more volatile than isophorone. Since Smyth et al. (1942) apparently assumed that the vapors generated were pure isophorone, the actual concentrations were lower than indicated above. Therefore, the dose-response data of Smyth et al. (1942) are seriously compromised.

Hazelton Labs, Inc. (1968) conducted a subchronic inhalation study of isophorone for Exxon Chemical Americas. Groups of 10 male and 10 female young adult Charles River CD rats were exposed to isophorone at air concentrations of 0 or 0.25 mg/l (250 mg/m³), 6 hours/day, 5 days/week for 4 weeks. Results of daily spectroscopic determinations indicated that the average daily exposure was 0.208 mg/l (208 mg/m³). Body weight measurements and hematological studies were made before exposure and after 4

weeks. The rats were killed and gross necropsy was performed. Organ weights were determined for lungs, liver, kidneys, adrenals and spleen. Histological examination of those tissues were performed in three males and three females per group. The following effects were observed: transient nasal bleeding, increased percentages of lymphocytes, decreased percentages of neutrophils and increased hemoglobin concentration in males and females and significantly lower terminal body weights and significantly decreased absolute and relative liver weights of exposed males, compared with controls.

5.6. OTHER RELEVANT INFORMATION

Reported values for the acute oral LD_{50} of isophorone in rats range from 1000-3450 mg/kg (Union Carbide and Carbon Corp., n.d.; Dow Chemical Co., 1962; Hazelton Labs, Inc. 1964a,b; Smyth et al., 1969, 1970; Bukhalovskii and Shugaev, 1976). The inhalation LC_{50} in rats was reported to be 7000 mg/m^3 (5700-8600 mg/m^3 , 95% confidence limits) for 4 hours (Hazelton Labs, Inc., 1965a). Dermal LD_{50} values for rabbits were reported to be 1380 mg/kg (Union Carbide and Carbon Corp., n.d.) and >3160 mg/kg (Hazelton Labs, Inc., 1964a,b).

Silverman et al. (1946) found that exposure in an inhalation chamber to 25 ppm (141 mg/m^3) for 15 minutes produced eye, nose and throat irritation in a majority of human subjects (12/exposure), while 10 ppm (57 mg/m^3) was tolerable for 8 hours. Hazelton Labs, Inc. (1965b) studied the sensory irritation thresholds in a group of six human subjects exposed for 7 minutes in an aerosol chamber. The odor threshold was <100 mg/m^3 , the eye and nose irritation thresholds were <359 mg/m^3 and the throat irritation threshold was <199 mg/m^3 .

5.7. SUMMARY

In a peer-reviewed draft of an NTP (1985) 103-week gavage study, it was concluded that there was some evidence that isophorone was carcinogenic to rats. The conclusion was based on findings of increased incidences of the relatively rare renal tubule cell adenomas and adenocarcinomas in male rats treated with 250 and 500 mg/kg/day, 5 days/week and the rare preputial gland carcinomas in males treated with 500 mg/kg/day, 5 days/ week. NTP (1985) concluded that there was equivocal evidence that isophorone was carcinogenic to mice because of the marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system in male mice treated with 500 mg/kg/day, 5 days/week and malignant lymphomas in male mice treated with 250 mg/kg/day, 5 days/week.

Isophorone was negative for reverse mutation in four strains of Salmonella typhimurium and for chromosome aberrations in Chinese hamster ovary cells in the presence or absence of S-9 (NTP, 1985). Negative results were also obtained for the micronucleus test in male and female mice and for UDS in primary rat hepatocytes (CMA, 1984). A positive response was obtained for SCE in Chinese hamster ovary cells in the absence, but not in the presence of S-9 (NTP, 1985). Although CMA (1984) obtained negative results for forward mutation using mouse lymphoma cells in the presence and absence of S-9, NTP (1985) found a slight positive response in the same assay in the absence of S-9 at much higher concentrations of isophorone.

No fetotoxic or teratogenic effects were observed in the offspring of rats and mice exposed by inhalation to isophorone at 0, 25, 50 or 115 ppm (0, 141, 283 or 650 mg/m³), 6 hours/day on days 6-15 of gestation.

In addition to the carcinogenic effects observed in rats and mice, NTP (1985) also found nonneoplastic effects of chronic oral exposure to isophorone. Compound-related reduced survival was observed in high-dose male

rats. Increased incidences of kidney lesions consisting of tubular cell and renal pelvis epithelial hyperplasia, tubule mineralization and nephropathy, were observed at both doses in both sexes of rats. Dose-related increased incidences of fatty metamorphosis of the adrenal cortex in male rats and focal hyperplasia of the anterior pituitary in female rats were also considered to be treatment-related. Treated mice (both doses) had increased incidences of coagulative necrosis and hepatocytomegaly in the liver, hyperkeratosis of the forestomach and focal hyperplasia of the pituitary. High dose mice had increased incidences of chronic focal inflammation of the kidney. In a 13-week preliminary gavage study, no treatment-related effects were observed in rats treated at ≤ 500 mg/kg/day, 5 days/week (NTP, 1985). At 1000 mg/kg/day, some female rats and mice died. Rats were lethargic immediately after dosing with 1000 mg/kg, but not mice. In a 90-day study, male rats exposed to 3000 ppm isophorone in the diet (250.5 mg/kg/day) had a significant, treatment-related decrease in mean body weight gain after 6 weeks; there was no effect on food consumption (AME, Inc., 1972a). No effects were observed at ≤ 1500 ppm (≤ 170.4 mg/kg/day). In dogs treated with 0, 35, 75 or 150 mg/kg/day of isophorone in gelatin capsules for 90 days, the only effect was soft and loose stools of dogs treated at 75 or 150 mg/kg/day. Values for the acute oral LD_{50} of isophorone in rats range from 1000-3450 mg/kg (Union Carbide and Carbon Corp., n.d.; Dow Chemical Co., 1962; Hazelton Labs, Inc., 1964a,b; Smyth et al., 1969, 1970; Bukhalovskii and Shugaev, 1976).

Subchronic inhalation exposure of rats and guinea pigs to isophorone at concentrations ≥ 100 ppm (≥ 565 mg/m³), 8 hours/day, 5 days/week for 6 weeks was associated with death, severe kidney and lungs lesions and poor growth (Smyth et al., 1942). Liver and kidney lesions were also observed at 50 ppm

(283 mg/m³); no effects were observed at 25 ppm (141 mg/m³). As discussed by U.S. EPA, (1980a), subsequent evaluation of this study revealed that the isophorone used by Smyth et al. (1942) was impure; therefore, the dose-response data are seriously compromised. Inhalation exposure of rats to 0.208 mg/l (208 mg/m³), 6 hours/day, 5 days/week for 4 weeks was associated with transient nasal bleeding, hematological changes, decreased body weight gain and decreased absolute and relative liver weights (Hazelton Labs, Inc., 1968). The inhalation LC₅₀ in rats was reported to be 7000 mg/m³ for 4 hours (Hazelton Labs, Inc., 1965a).

Inhalation exposure to 25 ppm (141 mg/m³) for 15 minutes produced eye, nose and throat irritation in humans; 10 ppm (57 mg/m³) was tolerable for 8 hours (Silvermann et al., 1946). Hazelton Labs, Inc. (1965b) found that the odor threshold was <100 mg/m³, the eye and nose irritation thresholds were <359 mg/m³ and the throat irritation threshold was <199 mg/m³ for six humans exposed for 7 minutes to isophorone in an aerosol chamber.

6. AQUATIC TOXICITY

6.1. ACUTE

In a flowthrough test, Cairns and Nebeker (1982) reported 96-hour LC_{50} values of 145 and 255 mg/l isophorone in juvenile fathead minnows, Pimephales promelas, depending upon the age of fish used. Union Carbide Corp. (1983) reported 24-, 48- and 96-hour LC_{50} values of 195, 195 and 185 mg/l, respectively, in a static test.

Buccafusco et al. (1981) reported 24- and 96-hour LC_{50} values of 240 and 220 mg/l, respectively, in bluegills, Lepomis macrochirus, in a static test, while U.S. EPA (1980a) cited a 96-hour LC_{50} of 224 mg/l in bluegills.

The sheepshead minnow, Cyprinodon variegatus, a marine shellfish, has been used in several studies. Heitmuller et al. (1981) determined that the 24- to 96-hour LC_{50} values were >170 mg/l but <300 mg/l in a static test. No fish died at 170 mg/l. Ward et al. (1981) calculated the 96-hour LC_{50} for juvenile sheepshead minnows to be 140 mg/l in a flow-through test. U.S. EPA (1980a) reported that the 96-hour LC_{50} in this species ranged from 166-295 mg/l.

LeBlanc (1980) found that the 24- and 48-hour LC_{50} values in Daphnia magna were 430 and 120 mg/l, respectively, in a static test. The "no discernible effect concentration" was 15 mg/l. U.S. EPA (1980a) reported a 48-hour EC_{50} of 117 mg/l in an unspecified effect in Daphnia magna. The 96-hour LC_{50} for the mysid shrimp, Mysidopsis bahia, was reported to be 12.9 mg/l (U.S. EPA, 1980a). The 24-hour LC_{50} in brine shrimp, Artemia salina, was 430 mg/l in a static test (Price et al., 1974).

6.2. CHRONIC

In a 35-day flowthrough embryo-larval test with fathead minnows, (Cairns and Nebeker, 1982), survival was affected at 112 mg/l but not at 56 mg/l. Growth in terms of full length was depressed at concentrations ≥ 30 mg/l. Growth in terms of body weight was depressed at ≥ 19 mg/l while, at 11 mg/l, fish were apparently unaffected; the authors determined the NOEC to be 14 mg/l, the geometric mean of 11 and 19 mg/l.

Lemke et al. (1983) conducted two flowthrough embryo-larval bioassays with fathead minnows, and determined no-effect levels for growth inhibition of 19.5 and 6.89 mg/l in the first and second bioassay, respectively.

Ward et al. (1981) conducted a similar flowthrough embryo-larval test with sheepshead minnows. The test began using eggs and continued until 28 days after hatching. Results are reported in terms of effects observed at a nominal concentration with the measured concentration in parentheses. At 476 mg/l (287 mg/l), all fish died by day 28. Growth (in terms of standard length) of juveniles at 238 mg/l (156 mg/l) was significantly lower than controls. The estimated MATC for embryos and juveniles was >80 and <156 mg/l based on growth. The chronic value for sheepshead minnows in an embryo-larval test was reported to be 110 mg/l by U.S. EPA (1980a).

6.3. PLANTS

The only information available about the toxicity of isophorone to aquatic plants was provided by U.S. EPA (1980a). The 96-hour EC_{50} values for reduction of cell numbers and inhibition of chlorophyll *a* were 122 and 126 mg/l, respectively, in the freshwater alga Selenastrum capricornutum and 105 and 110 mg/l, respectively, in the saltwater alga Skeletonema costatum.

6.4. RESIDUES

Barrows et al. (1980) investigated the uptake of isophorone by bluegills. Fish were exposed to an average water concentration of 0.092 mg/l isophorone in a flowthrough system. An apparent equilibrium was attained after 14 days. The BCF, defined as the mean measured residues in fish tissues (whole body) divided by the mean water concentration, was 7. The half-life for isophorone in bluegill tissues was 1 day.

6.5. SUMMARY

Acute LC_{50} or EC_{50} values for freshwater and marine species were generally 100-400 mg/l, with the exception of mysid shrimp, Mysidopsis bahia, which was unusually sensitive (96-hour LC_{50} = 12.9 mg/l) (U.S. EPA, 1980a). NOECs for growth reduction in chronic embryo-larval tests were 14 mg/l for fathead minnows (Cairns and Nebeker, 1982) and 80-156 mg/l in sheepshead minnows (Ward et al., 1981). The NOEC for unspecified effects in Daphnia magna was 15 mg/l (Leblanc, 1980). Based on the limited information available, 15 mg/l isophorone appears to be a NOEC in freshwater fish and invertebrates. Isophorone is not bioaccumulated in bluegills to a great extent, having a 14-day BCF of 7 and a half-life of 1 day (Barrows et al., 1980).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1978) recommended a maximum permissible exposure limit of 4 ppm (23 mg/m³) as a TWA concentration for up to a 10-hour workshift. The recommendation was based on the report of Ware (1973) that workers at Western Electric Company complained of fatigue and malaise at 5-8 ppm (28-45 mg/m³), but not at 1-4 ppm (6-23 mg/m³).

The OSHA standard for occupational exposure is 25 ppm (140 mg/m³) as an 8-hour TWA concentration limit in the workroom air (Code of Federal Regulations, 1981).

The ACGIH (1984) has adopted a ceiling limit of 5 ppm (~25 mg/m³) for occupational exposure to isophorone. The ceiling limit was recommended by the ACGIH (1980) based on the report of Ware (1973).

Under the Federal Food, Drug and Cosmetic Act, isophorone has been exempted from the requirement of a tolerance when used as a solvent and cosolvent for pesticide formulations used before crops emerge from soil, for post-emergence use on rice before the crop begins to head and on sugar and table beets (U.S. EPA, 1974).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of isophorone could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

The report of a 2-year chronic gavage study of isophorone for carcinogenicity (NTP, 1985) was available as a peer-reviewed draft. The results of this study were summarized in Table 5-1. NTP (1985) concluded that there was some evidence that isophorone was carcinogenic to rats based on findings of increased incidences of the relatively rare renal tubule cell adenomas and adenocarcinomas in male rats treated with 250 and 500 mg/kg/day, 5 days/week and the rare preputial gland carcinomas in males treated with 500 mg/kg/day, 5 days/week. NTP (1985) concluded that there was equivocal evidence that isophorone was carcinogenic to mice because of the marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system in male mice treated with 500 mg/kg/day, 5 days/week and malignant lymphomas in male mice treated with 250 mg/kg/day, 5 days/week.

Isophorone was negative for reverse mutation in four strains of Salmonella typhimurium and for chromosome aberrations in Chinese hamster ovary cells in the presence or absence of S9 (NTP, 1985). Negative results were also obtained for the micronucleus test in male and female mice and for UDS in primary rat hepatocytes (CMA, 1984). A positive response was obtained for SCE in Chinese hamster ovary cells in the absence, but not in the presence of S9 (NTP, 1985). Although CMA (1984) obtained negative results for forward mutation using mouse lymphoma cells in the presence and absence of S9, NTP (1985) found a slight positive response in the same assay in the absence of S9 at much higher concentrations of isophorone.

No fetotoxic or teratogenic effects were observed in the offspring of rats and mice exposed by inhalation to isophorone at 0, 25, 50 or 115 ppm (0, 141, 282 or 650 mg/m³), 6 hours/day on days 6-15 of gestation.

In addition to the carcinogenic effects observed in rats and mice, NTP (1985) also found nonneoplastic effects of chronic oral exposure to isophorone. Compound-related reduced survival was observed in high-dose male rats. Increased incidences of kidney lesions consisting of tubular cell and renal pelvis epithelial hyperplasia, tubule mineralization and nephropathy, were observed at both doses in both sexes of rats. Dose-related increased incidences of fatty metamorphosis of the adrenal cortex in male rats and focal hyperplasia of the anterior pituitary in female rats were also considered to be treatment-related. Treated mice (both doses) had increased incidences of coagulative necrosis and hepatocytomegaly in the liver, hyperkeratosis of the forestomach and focal hyperplasia of the pituitary. High dose mice had increased incidences of chronic focal inflammation of the kidney. In a 13-week preliminary gavage study, no treatment-related effects were observed in rats treated at ≤ 500 mg/kg/day, 5 days/week (NTP, 1985). At 1000 mg/kg/day, some female rats and mice died. Rats, but not mice, were lethargic immediately after dosing with 1000 mg/kg. In a 90-day study, male rats exposed to 3000 ppm isophorone in the diet (250.5 mg/kg/day) had a significant, treatment-related decrease in mean body weight gain after 6 weeks; there was no effect on food consumption (AME, Inc., 1972a). No effects were observed at ≤ 1500 ppm (≤ 170.4 mg/kg/day). In dogs treated with 0, 35, 75 or 150 mg/kg/day of isophorone in gelatin capsules for 90 days, the only effect was soft and loose stools of dogs treated at 75 or 150 mg/kg/day (AME, Inc., 1972b).

Subchronic inhalation exposure of rats and guinea pigs to isophorone at concentrations ≥ 100 ppm (>565 mg/m³), 8 hours/day, 5 days/week for 6 weeks was associated with death, severe kidney and lung lesions and poor growth (Smyth et al., 1942). Liver and kidney lesions were also observed at 50 ppm

(283 mg/m³); no effects were observed at 25 ppm (141 mg/m³). As discussed by U.S. EPA (1980a), subsequent evaluation of this study revealed that the isophorone used by Smyth et al. (1942) was impure; therefore, the dose-response data are seriously compromised. Inhalation exposure of rats to 0.208 mg/l (208 mg/m³), 6 hours/day, 5 days/week for 4 weeks was associated with transient nasal bleeding, hematological changes, decreased body weight gain and decreased absolute and relative liver weights (Hazelton Labs., Inc., 1968).

Since isophorone appeared to be carcinogenic to rats and mice (NTP, 1985), it is appropriate to derive a q_1^* to estimate the increased lifetime risk of human exposure to isophorone. As seen from Table 5-1, the preputial gland carcinomas in male rats and the hepatic and integumentary system tumors in male mice were observed in overall incidences that were significantly increased above controls (Fisher Exact test) and showed a significant positive dose-related trend (Cochran-Armitage test). The rare kidney tumors of male rats also indicated some evidence of carcinogenicity. Although the incidence of kidney tumors was low, the occurrence was noteworthy because kidney tumors were rarely observed in historical controls (4/1091); direct comparison of the incidences in the low and high dose groups with historical controls indicated a significant increase ($p=0.002$) by the Fisher Exact test (NTP, 1985). These data are the most appropriate for q_1^* determination.

The incidences of hepatocellular adenoma or carcinoma (combined) and the integumentary system tumors in male mice showed significantly positive dose-related trends and were significantly greater than controls in the high dose group. Therefore, these data appear to be the most appropriate for q_1^* determination. Although the incidence of malignant lymphomas in low-dose

male mice was significantly higher than controls by the Fisher Exact test, the incidence in high-dose males was lower than controls, and a negative dose-related trend was indicated. Therefore, malignant lymphomas will not be included in the q_1^* determination.

According to U.S. EPA (1984), "to obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation." Since NTP (1985) provided individual animal tumor pathology data, it is possible to pool the male rats that had at least one kidney or preputial tumor without counting twice the rat that had a renal and preputial tumor. The pooled incidences and other data used to calculate the q_1^* are presented in Table 8-1.

The transformed doses were calculated by multiplying the doses of 250 and 500 mg/kg/day by 5 days/7 days and by 103 weeks/105 weeks. The unadjusted q_1^* was calculated using the computerized multistage model, GLOBAL 82, developed by Howe and Crump (1982). The human q_1^* value of 4.1×10^{-8} (mg/kg/day) $^{-1}$ was calculated by multiplying the unadjusted value by the cube root of the ratio of the reference human body weight of 70 kg to the mouse body weight. This q_1^* of 4.1×10^{-8} (mg/kg/day) $^{-1}$ is recommended for estimating the increased lifetime risk for human exposure to isophorone.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: isophorone

Reference: NTP, 1985

Species, Strain, Sex: rat, Fischer 344/N, male

Body weight: 0.40 kg (measured)

Length of exposure (t_e) = 103 weeksLength of experiment (t_e) = 105 weeksLifespan of animal (L) = 105 weeks

Tumor site and type: kidney (tubular cell) adenoma or carcinoma; preputial gland carcinoma

Route, vehicle: gavage, corn oil

Experimental Doses or Exposures (mg/kg/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/48
250	175	3/50
500	350	8/50

Unadjusted q_1^* from study = 7.33×10^{-4} (mg/kg/day) $^{-1}$ Human q_1^* = 4.1×10^{-3} (mg/kg/day) $^{-1}$

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Studies of chronic and subchronic oral and inhalation exposure of animals to isophorone were discussed in Section 5.5., and the toxicity data are summarized in Table 9-1. In addition, an inhalation teratology study in mice and rats (CMA, 1984; U.S. EPA, 1985) was available; however, no fetotoxic or teratogenic effects were observed in the offspring of the dams exposed to ≤ 115 ppm (≤ 650 mg/m³), 6 hours/day on days 6-15 of gestation. Therefore an MED for fetotoxicity or teratogenicity cannot be calculated.

As seen from Table 9-1, adequate data for chronic oral exposure to isophorone were available; therefore, the subchronic oral studies need not be considered for RQ determination. Since no chronic inhalation data were available, however, the subchronic data of Hazelton Labs, Inc. (1968) will be considered. The transformed doses were calculated by expanding the exposure over a 24-hour day and 7 days/week, by multiplying by the inhalation rate of the rats and by dividing by the rat body weight. The average body weights of the male and female rats were supplied by the investigators (see Table 9-1). The inhalation rates (I) in m³/day were calculated according to the equation prescribed by U.S. EPA (1980b):

$$I = 0.105 (\text{body weight}/0.113)^{2/3}$$

The subchronic inhalation study by Smyth et al. (1942) cannot be used for RQ determination because the isophorone used in this study was impure, precluding the adequate correlation of dose with response (U.S. EPA, 1980a).

Data used to calculate CSs are presented in Table 9-2. The MEDs were calculated by multiplying the animal dose by the cube root of the ratio of the animal body weight (see Table 9-1) to the human body weight of 70 kg and multiplying by 70 kg to express the MED as mg/day.

TABLE 9-1
Toxicity Summary for Isophorone

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral	rat/CEE	M	20	0.256 ^a	diel	NR	3000 ppm, 90 days	250.5 ^a	Significantly reduced body weight gain, no ef- fect on food consumption	AME, Inc., 1972a
Oral (gavage)	rat/T344	F	10	0.13 ^a	corn oil	94-97%	1000 mg/kg/day, 5 days/week, for 13 weeks	714.3 ^b	Death of one rat	NTP, 1985
Oral (gavage)	rat/T344	M	50/ group	0.40 ^a	corn oil	94-97%	250 and 500 mg/kg/day, 5 days/week for 103 weeks	179 and 357 ^b	Increased mortality at 357 mg/kg/day; increased incidence of renal tubule cell mineralization and hyperplasia at 179 and 357 mg/kg/day; dose- related increased inci- dence of fatty meta- morphosis of adrenal cortex at ≥ 179 mg/kg/day	NTP, 1985
Oral (gavage)	rat/T344	F	50/ group	0.25 ^a	corn oil	94-97%	250 and 500 mg/kg/day, 5 days/week for 103 weeks	179 and 357 ^b	Increased incidence of renal tubule cell hyper- plasia at 357 mg/kg/day; increased incidence of nephropathy at 179 and 357 mg/kg/day; dose-re- lated increased incidence of focal hyperplasia of anterior pituitary at ≥ 179 mg/kg/day	NTP, 1985
Oral (gavage)	mouse/ B6C3F1	F	10	0.02 ^a	corn oil	94-97%	1000 mg/kg/day, 5 days/week for 13 weeks	714.3 ^b	Death of 3 mice	NTP, 1985
Oral (gavage)	mouse/ B6C3F1	M	50/ group	0.045 ^a	corn oil	94-97%	250 and 500 mg/kg/day, 5 days/week for 103 weeks	179 and 357 ^b	Increased incidences of coagulative necrosis and hepatocytomegaly in liver and hyperkeratosis of forestomach at 179 and 357 mg/kg/day; increased incidence of chronic focal inflammation of the kidney at 357 mg/kg/day	NTP, 1985

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral (gavage)	mouse/ B6C3F1	F	50/ group	0.030 ^a	corn oil	95-97%	250 and 500 mg/kg/day, 5 days/week for 103 weeks	179 and 357 ^b	Slight (5%) decrease in body weight gain and in- creased incidence of hyper- keratosis of forestomach at 357 mg/kg/day; in- creased incidence of focal hyperplasia of the pituitary at 179 and 357 mg/kg/day	MTP, 1965
Oral	dog/beagle	M&F	4/sex group	12.7 ^c	gelatin capsule	NR	75 or 150 mg/kg/day for 90 days	75 or 150	Soft and loose stools	AME, Inc., 1972 ^b
Inhalation	rat/Mistar or guinea pig/NR	M	10/ group	0.35 ^c	vapor in air	commercial grade, questionable purity	50, 100, 200 and 500 ppm (283, 565, 1130 and 2826), 8 hours/day, 5 days/week for 6 weeks	not calculated ^d	Increased incidences of liver and kidney pathology at ≥50 ppm; poor growth and increased mortality at ≥100 ppm; nose and eye irritation, hematological changes and albuminuria 500 ppm	Smyth et al., 1942
Inhalation	rat/CD	M	10	0.250 ^a	air	assumed to be free from impurities	208 mg/m ³ , 6 hours/day, 5 days/week for 4 weeks	26.2 ^e	Transient nasal bleed- ing, increased lympho- cytes, decreased neutro- phils, increased hemo- globin, reduced body weight gain, reduced absolute and relative liver weight	Hazellon Labs, Inc., 1968
Inhalation	rat/CD	F	10	0.207 ^a	air	assumed to be free from impurities	208 mg/m ³ , 6 hours/day, 5 days/week for 4 weeks	28.2 ^e	Transient nasal bleed- ing, increased lympho- cytes, decreased neutro- phils, increased hemoglobin	Hazellon Labs, Inc., 1968

^aValues supplied by the investigators or calculated from data supplied by the investigators^bCalculated by multiplying by 5 days/7 days^cAssumed^dNo transformed doses were calculated because, as discussed by U.S. EPA (1980a), the isophorone used by Smyth et al. (1942) was impure; therefore the exposure concentrations were lower and the dose-response data are seriously compromised.^eSee text

TABLE 9-2
Composite Scores for Isophorone

Route	Species/Sex	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV _d	Effect	RV _e	CS	RQ	Reference
Oral	rat/M	179	2240	1	Increased incidence of renal tubule cell mineralization; fatty metamorphosis of adrenal cortex	7	7	1000	MTP, 1985
Oral	rat/f	179	1915	1	Increased incidences of nephro- pathy and focal hyperplasia of anterior pituitary	6	6	1000	MTP, 1985
Oral	rat/M	357	4468	1	Increased mortality	10	10	1000	MTP, 1985
Oral	mouse/M	179	1081	1	Coagulative necrosis of liver, hyperkeratosis of forestomach	6	6	1000	MTP, 1985
Inhalation	rat/M	26.2	28.3*	3.3	Decreased body weight gain; decreased absolute and relative liver weight; hematological changes	4	13.2	1000	Hazleton Labs. Inc., 1968

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure

In rats treated orally with transformed doses ≥ 179 mg/kg/day, males had increased incidences of renal tubule cell mineralization and hyperplasia in the kidney and fatty metamorphosis of the adrenal cortex, while female rats had increased incidences of nephropathy and hyperplasia of the anterior pituitary (NTP, 1985). The renal tubule cell mineralization warrants an RV_e of 7 while the increased incidence of nephropathy, as a treatment-related acceleration of an age-related process, warrants an RV_e of 6. The dose of 179 mg/kg/day is equivalent to a human MED of 2240 mg/day, calculated using the male rat body weight, or to a human MED of 1915 mg/day, calculated using the female rat body weight. Both MEDs, however, correspond to RV_d s of 1, since $\log$ MED is ≥ 3 . Multiplying the RV_d s by the RV_e s results in CSs of 7 and 6, both of which correspond to RQs of 1000.

Male rats treated orally with 357 mg/kg/day had a treatment-related increased mortality (NTP, 1985) an effect which has an RV_e of 10. The MED is 4468 mg/day, corresponding to an RV_d of 1. The CS of 10 corresponds to an RQ of 1000.

In mice treated orally with transformed doses of ≥ 179 mg/kg/day, males had increased incidences of coagulative liver necrosis and hyperkeratosis of the forestomach, while females had focal hyperplasia of the pituitary. At 357 mg/kg/day, female mice had hyperkeratosis of the forestomach. The highest RV_e that can be assigned to these effects is 6 for hyperkeratosis and necrosis. The MED using the male mice data is 1081 mg/day, which corresponds to an RV_d of 1. The CS is 6, corresponding to an RQ of 1000.

In rats treated subchronically by inhalation with transformed doses of 26.2 mg/kg/day for males and 28.2 mg/kg/day for females, increased percentages of lymphocytes, decreased percentages of neutrophils and increased hemoglobin concentrations were observed (Hazelton Labs, Inc., 1968). Male

rats also had reduced body weight gain and reduced absolute and relative liver weights. The equivalent human doses calculated from these animal doses are both 283 mg/day. Because the exposure was subchronic and no information regarding the effects of chronic inhalation exposure was available, it is necessary to divide the human dose by 10 to yield an MED of 28.3 mg/day. The RV_d is 3.3. The highest RV_e that can be assigned for the hematological effects and reduced body and liver weights is 4. Multiplying the RV_d by the RV_e results in a CS of 13.2, which corresponds to an RQ of 1000.

As seen from Table 9-2, all the CSs correspond to an RQ of 1000; however, the highest CS was obtained from the subchronic inhalation data of Hazelton Labs, Inc. (1968), which is recommended as the basis of the RQ for isophorone (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

An NTP (1985) carcinogenesis study of isophorone in rats and mice was available as a peer-reviewed draft. In this study, groups of 50 male and 50 female Fischer 344/N rats and 50 male and 50 female B6C3F1 mice were treated by gavage with isophorone in corn oil at 0, 250 or 500 mg/kg/day, 5 days/week for ~2 years. The results of this study are summarized in Table 5-1. No increased tumor incidences were observed in female rats or mice. NTP (1985) concluded that there was some evidence that isophorone was carcinogenic to rats based on findings of increased incidences of the relatively rare renal tubule cell adenomas and adenocarcinomas in male rats treated with 250 and 500 mg/kg/day, 5 days/week and the rare preputial gland carcinomas in males treated with 500 mg/kg/day, 5 days/week. NTP (1985) concluded that there was equivocal evidence that isophorone was carcinogenic to mice because of the marginally increased incidences of hepatocellular

TABLE 9-3

Isophorone

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	28.3 mg/day
Effect:	reduced body weight; reduced absolute and relative liver weight; hematological changes
Reference:	Hazeltan Labs, Inc., 1968
RV _d :	3.3
RV _e :	4
Composite Score:	13.2
RQ:	1000

*Equivalent human dose

tumors and mesenchymal tumors of the integumentary system in male mice treated with 500 mg/kg/day, 5 days/week and malignant lymphomas in male mice treated with 250 mg/kg/day, 5 days/week.

Studies relating human exposure to carcinogenic effects could not be located in the available literature. Therefore, the evidence that isophorone is carcinogenic to animals is sufficient to classify isophorone as a Group C chemical, according to the scheme of IARC.

Since isophorone appeared to be carcinogenic to rats and mice (NTP, 1985), it is appropriate to derive a potency factor (F). As seen from Table 5-1, the tumor types that were observed in overall incidences that were significantly increased above controls (Fisher Exact test) and showed a significant positive dose-related trend (Cochran-Armitage test) were the preputial gland carcinomas in male rats and the rare kidney tumors of male rats also indicated some evidence of carcinogenicity. Although the incidence of kidney tumors in rats was low, the occurrence was noteworthy because kidney tumors were rarely observed in historical controls (4/1091); direct comparison of the incidences in the low- and high-dose groups with historical controls indicated a significant increase ($p=0.002$) by the Fisher Exact test (NTP, 1985). These data are the most appropriate for deriving an F factor.

Since NTP (1985) provided individual animal tumor pathology, it is possible to pool the male rats that had at least one kidney or preputial tumor without counting twice the rat that had a renal and preputial tumor. The pooled incidences and other data used to calculate F are presented in Table 9-4.

The transformed doses were calculated by multiplying the doses of 250 and 500 mg/kg/day by 5 days/7 days and by 103 weeks/105 weeks. The unadjusted $1/ED_{10}$ was calculated using the computerized multistage model developed by Howe and Crump (1982). The F factor of 2.22×10^{-3} (mg/kg/day) $^{-1}$ was calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of the reference human body weight (70 kg) to the animal body weight.

Since the F factor is <1 , isophorone is placed in Potency Group 4. A Potency Group 4 chemical with an IARC classification of C ranks LOW in the Hazard Ranking Scheme under CERCLA.

TABLE 9-4
Derivation of Potency Factor (F) for Isophorone

Reference:	NTP, 1985		
Exposure route:	oral, gavage		
Species:	rat		
Strain:	Fischer 344/N		
Sex:	male		
Vehicle or physical state:	corn oil		
Body weight:	0.40 kg		
Duration of treatment:	103 weeks		
Duration of study:	105 weeks		
Lifespan of animal:	105 weeks		
Target organ:	kidney and preputial gland		
Tumor type:	tubular cell adenoma or carcinoma and preputial gland carcinomas		
	<u>mg/kg/day, 5 days/week</u>		
Experimental Doses or Exposures:	0	250	500
Transformed Doses: (mg/kg/day)	0	175	350
Tumor incidences:	0/48	3/50	8/50
Unadjusted 1/ED ₁₀ :	3.96x10 ⁻² (mg/kg/day) ⁻¹		
Adjusted 1/ED ₁₀ : (F factor)	2.22x10 ⁻² (mg/kg/day) ⁻¹		

150-270-20-11C

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in August, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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